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Environmental Tobacco Smoke Exposure and Heart Disease: A Critique of the Claims of Glantz and Parmley

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ABSTRACT

Background — A review by Glantz and Parmley published in 1995 and subsequently widely cited claims to demonstrate that passive smoke exposure increases the risk of heart disease. We have critically examined this claim in the light of the published evidence which they cite and of more recent publications.

Methods and results — An updated review of the epidemiological evidence reveals no association between heart disease and ETS exposure in the workplace. Claims of an association with spousal smoking are weakened by the existence of various forms of bias in the studies. They are also undermined by recent reports from three large studies without evident major weaknesses which find essentially no association with spousal smoking. Interpretation of the experimental clinical studies is problematic because it is not possible to expose humans to ETS without their knowledge. For several reasons, short-term effects of exposure to unrealistically high concentrations of ETS throw no useful light on risk of coronary atherogenesis from long-term realistic exposure. In particular, the fact that humans can adapt to reduced ambient oxygen availability needs to be allowed for. Effects of counts of anuclear endothelial cell carcasses in circulating blood after ETS exposure are uninterpretable without basic information on the significance of this endpoint. The need for a realistic animal model for coronary atherosclerosis is not fulfilled by short-term studies in rats, rabbits, hamsters, birds or dogs in which aortic atheromatous plaque formation is used as a surrogate endpoint. Stress from confinement within cag-

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es, from the noise of fans and from irritation from high ETS concentrations needs to be controlled for, particularly in experiments on rabbits and birds. This has not been done and there is generally a serious dearth of information on the non-specific or specific effects of other environmental chemicals on many of the endpoints that have been used.

Studies on the possible role of platelets in the aetiology of coronary heart disease are difficult to interpret because of confusion between their possible long-term role in atherogenesis and their putative involvement in thrombus formation which results in myocardial infarction. Evidence from an inadequately designed one-day study involving persons exposed to unmeasured amounts of ETS in a hospital corridor provides no insight into mechanisms involved in coronary atherogenesis. A study of the effect of exposure to ETS on the diameter of the brachial artery diameter is open to criticism because of the way in which subjects were recruited and failure to control for potentially important confounders.

Conclusion — The available experimental and epidemiological evidence does not justify a conclusion that ETS exposure increases the risk of heart disease.

Key Words: Atherogenesis, Carbon monoxide, Nicotine, Spousal smoking, Workplace exposure, Animal models.

INTRODUCTION

Epidemiological and experimental evidence relating to a possible relationship between heart disease and environmental tobacco smoke (ETS) exposure has been steadily accumulating over the last 20 years. Earlier reports, *e.g.*, by the US Surgeon General (1986) and by the National Research Council (1986), considered the evidence inconclusive. However, some more recent reports (Glantz and Parmley, 1991; 1995; 1996; Taylor and Johnson, 1992; Law *et al.*, 1997; California EPA, 1997), although not all (Australian NHMRC, 1997), have concluded that ETS exposure is an important cause of heart disease.

A particularly influential and very widely cited report has been Glantz and Parmley (1995). That report concluded that "the ETS experienced by many people in their daily lives is enough to produce substantial adverse effects on the cardiovascular system" and cited estimates of 30,000 to 60,000 deaths annually in the United States as the population burden associated with passive smoking. The conclusions were based on two types of evidence. One was evidence based on 15 epidemiological studies, which provided a pooled estimate of 1.2 (95% confidence interval [CI], 1.1 to 1.4) for the relative risk of heart disease in never smokers associated with marriage to a smoker, and a somewhat larger estimate of 1.3 (95% CI 1.1 to 1.6) for the relative risk of nonfatal coronary events. The other was evidence mainly deriving from laboratory and clinical studies relating to a wide range of issues of possible relevance to heart disease. Glantz and Parmley (1995) included separate sections relating to (i) effects of ETS on oxygen, delivery, processing and exercise, (ii) platelets, (iii)

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atherosclerosis, (iv) free radicals in ETS and ischemic damage, and (v) myocardial infarction.

The purpose of this paper is to provide an updated review of the evidence on ETS and heart disease with particular reference to the claims of Glantz and Parmley. Our paper is divided into two sections. We start by providing a quantitative overview of all relevant epidemiological data published by the end of 1997. This overview now covers 22 studies including a number of recent studies of substantial size, notably the two large American Cancer Society (ACS) Cancer Prevention Studies CPS-I and CPS-II (LeVois and Layard, 1995; Steenland *et al.*, 1996). We then discuss in turn the other issues raised by Glantz and Parmley (extending the list also to include endothelium function, based on the recent study of Celermajer *et al.*, 1996). We examine in detail the basis for the interpretation put on the data by Glantz and Parmley, considering not only the evidence they cite, but also evidence from other relevant studies.

Finally, we discuss the overall evidence briefly and draw our own conclusions as to whether any relationship between ETS exposure and risk of heart disease has in fact been demonstrated.

EPIDEMIOLOGICAL EVIDENCE

The Studies

Table 1 summarizes the 22 studies providing evidence on the relationship between ETS exposure and heart disease risk. For each study, the table shows the main literature reference, where the study was conducted, the type of study (case-control, cross-sectional or prospective), whether the study provided evidence on fatal, hospitalized or other non-fatal heart disease and the number of heart disease cases among lifelong nonsmokers that the study provides evidence on. Glantz and Parmley (1995) had considered all the studies in Table 1 published before 1994 and also two earlier reports on the Chinese study of He et al. (1989; 1994).

For a major disease and a claimed risk factor of potential importance, it is surprising that results have never been reported in a peer-reviewed published paper for as many as seven of these studies. Thus, four studies were reported only in abstracts (Martin *et al.*, 1986; Palmer *et al.*, 1988; Mannino *et al.*, 1995; Ciruzzi *et al.*, 1996), two were reported only in theses (Butler, 1988; Jackson, 1989) and one only in a letter (LaVecchia et al., 1993). As a result, full details of some studies are not available. From the material that is provided, a number of comments can be made about the nature of the studies.

- **Location:** Thirteen studies have been conducted in the USA, four in Western Europe, two each in Asia and Australasia and one in South America.

- **Study type:** There were ten prospective studies, nine case-control studies and three of cross- sectional design. In eight of the prospective studies, the endpoint was death from heart disease but in two (Svendsen *et al.*,

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Table 1. Epidemiological studies of ETS exposure and heart disease risk.

Study	Study location	Study type[a]	Endpoints studied[b]	Number of heart disease cases in lifelong nonsmokers[c]		
				Females	Combined	Males
Hirayama (1984)	Japan	P	F	494		
Garland *et al.* (1985)	USA/California	P	F	19		
Lee *et al.* (1986)	England	CC	H	77		41
Martin *et al.* (1986)	USA/Utah	CS	NF	23		
Svendsen *et al.* (1987)	USA	P	F, NF			69
Butler (1988)[d]	USA/California	P	F	80		
Palmer *et al.* (1988)	USA/?	CC	H			
Sandler *et al.* (1989)	USA/Maryland	P	F	988		370
Hole *et al.* (1989)	Scotland	P	F	55		65
Jackson (1989)	New Zealand	CC	F, NF	20		49
Humble *et al.* (1990)	USA/Georgia	P	F	76		
Dobson *et al.* (1991)	Australia	CC	F+NF	160		183
LaVecchia *et al.* (1993)	Italy	CC	H	44		69
Layard (1995)	USA	CC	F	914		475
LeVois and Layard (1995)[e]	USA	P	F	7133		7758
Mannino *et al.* (1995)	USA	CS	NF			
Muscat and Wynder (1995)	USA/4 cities	CC	H	46		68
Tunstall-Pedoe *et al.* (1995)	Scotland	CS	NF		428	

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Tunstall-Pedoe *et al.* (1995)	Scotland	CS	NF		428	

Table 1. Epidemiological studies of ETS exposure and heart disease risk. (continued)

Study	Study location	Study type[a]	Endpoints studied[b]	Number of heart disease cases in lifelong nonsmokers[c] Females	Combined	Males
Ciruzzi *et al.* (1996)	Argentina	CC	H		336	
He *et al.* (1996)	China	CC	H	78		
Steenland *et al.* (1996)	USA	P	F	1325		2494
Kawachi *et al.* (1997)	USA	P	F+NF	152		

[a] The study types are CC = case control, CS = cross-sectional and P = prospective.

[b] The endpoints are F = fatal heart disease, H = hospitalized heart disease and NF = non-fatal heart disease. F+NF implies combined data only available for fatal and non-fatal heart disease.

[c] Numbers of heart disease cases in lifelong nonsmokers are totals in the study; for analyses relating to specific types of exposure numbers may be less than this. Numbers were not available for Palmer *et al.* (1988) and Mannino *et al.* (1995). Numbers only provided for sexes combined for Tunstall-Pedoe *et al.* (1995) and Ciruzzi *et al.* (1996).

[d] Only results relating to the spouse-pairs cohort considered as the AHSMOG cohort included ex-smokers.

[e] Only results relating to CPS-I study considered as Steenland *et al.* (1996) provided updated results for CPS-II.

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1987; Kawachi *et al.*, 1997) onset of new non-fatal events was also included as an endpoint. There were four hospital case-control studies (Lee *et al.*, 1986; LaVecchia *et al.*, 1993; Muscat and Wynder *et al.*, 1995; Ciruzzi *et al.*, 1996) in which living heart disease cases were compared with appropriate hospital controls. In the Chinese case-control study (He *et al.*, 1996), hospital patients were compared with a mixture of population and hospital controls. In one hospital case-control study (Palmer *et al.*, 1988), the nature of the control group was not stated. In the two Australasian case-control studies (Jackson, 1989; Dobson *et al.*, 1991) both living and dead cases were compared with population controls. In one case-control study (Layard, 1995), both cases and controls were decedents. In the cross-sectional studies, subjects reported on presence or history of heart disease. In one of these (Tunstall-Pedoe et al., 1995), subjects also attended for clinical procedures, including ECG, which were used to detect previously undiagnosed cases of heart disease.

- **Number of cases:** Of the 20 studies reporting numbers of cases occurring in lifelong nonsmokers, seven involved less than 100 cases, nine involved 101-500 cases, and four involved more than 1000 cases. The largest study, CPS-I (LeVois and Layard, 1995) involved more cases, 14891, than all the remaining studies put together.

- **Sex:** Results were reported for females in 18 studies and for males in 11 studies. Three studies only reported findings for sexes combined.

- **Interviews:** Subjects were interviewed directly in all the prospective and cross-sectional studies and in many of the case-control studies. In the study of Jackson et al. (1989), data for 43% of cases and 34% of controls came from a study of coronary deaths and presumably would have been obtained from the next-of-kin. Dobson *et al.* (1991) obtained data by completely different methods for cases and controls, which could have led to bias. For cases, data were obtained from survivors by hospital interview and from decedents by medical records or mailed questionnaires, whereas all information was obtained directly for controls. The study by Layard et al. (1995) involved interviewing next-of-kin of decedents from heart disease (cases) and from causes not generally considered smoking-related (controls).

- **Confirmation of smoking status:** Although most studies used only one source of information to determine that the subject was a lifelong nonsmoker, Tunstall-Pedoe *et al.* (1995) used serum cotinine assays to confirm nonsmoking status, excluding subjects with a level above 17.5 ng/ml. Steenland *et al.* (1996) collected data from both husband and wife concerning both their own smoking habits and those of their spouse. However, no attempt was made to exclude subjects who reported never smoking themselves but whose spouse reported they had smoked.

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- **Data on potential confounding variables:** As can be seen from Table 2, the studies involved the collection of variable amounts of data on potential confounding variables. Nearly all studies adjusted for age and specifically restricted attention to married women and/or adjusted for marital status in the analyses of spousal smoking. The risk factors most often considered were blood pressure, cholesterol, social class/education/income and obesity/weight, each taken account of in about half the studies.

- **Study weaknesses:** Small study size and limited control for confounding variables in a number of studies, and failure to confirm nonsmoking status in most studies are weaknesses evident from the above. Other weaknesses (see Lee, 1992) include a seriously incomplete follow-up of deaths in two prospective studies (Hirayama, 1984; Sandler *et al.*, 1989) and failure to confirm reported ETS exposure from a separate source in most studies. In four studies (Hirayama, 1984; Garland *et al.*, 1986; Sandler *et al.*, 1989; He *et al.*, 1996) errors were made in presenting findings that were later corrected. The most obvious major weakness in a single study, as already pointed out, is the collection of data for cases and controls in a completely different way by Dobson *et al.* (1991). It should also be noted that Tunstall-Pedoe *et al.* (1995) asked subjects to report recent ETS exposure as "a lot", "some", "little", or "none", an index which was shown, using cotinine data, to produce results strongly affected by recall bias.

Indices of ETS exposure

Although there are some limited data available on other indices of ETS exposure, attention has been restricted to the two main sources, the spouse and the workplace. For spousal exposure, data for "spouse ever smoked" and "spouse current smoker" are considered separately, because Steenland et al. (1996) suggested that "spouse current smoker" was likely to be a more sensitive index of exposure than was "spouse ever smoked". In six studies (Sandler *et al.*, 1987; Hole *et al.*, 1989; Jackson, 1989; Dobson *et al.*, 1991; Mannino *et al.*, 1995; Kawachi *et al.*, 1997), data on at-home ETS exposure has been used in place of spousal exposure, which was not specifically studied. In one study (Tunstall-Pedoe *et al*, 1995) the data cited are for any ETS exposure in the past 3 days.

Relative Risks and 95% Confidence Limits

An attempt was made to extract all relevant risks and 95% confidence intervals (CIs) from the published sources for the three selected indices of ETS exposure. Where studies presented appropriate data on numbers of cases and controls for the various exposure categories, relative risks and 95% CIs were calculated, or checked, using the CIA program based on the methods described in Morris and Gardner (1988). Where studies presented relative risks and 95% CI for different levels of exposure, these were combined, taking account of the non-independence of these estimates due to their having a com-

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Table 2. Relative risk estimates (95% CI) for heart disease among lifelong nonsmokers.

Study	Sex	Relative risk (95% CI) Spouse ever smoked	Spouse current smoker	Workplace exposure	Covariates adjusted for[a]
Hirayama (1984)	F	1.16 (0.94–1.43)			a,m
Garland *et al.* (1986)	F	2.70 (0.70–10.50)	2.25 (0.31–16.24)		a,b,c,m,o
Lee *et al.* (1986)[b]	F	0.93 (0.54–1.62)		0.69 (0.26–1.87)	a,m
	M	1.24 (0.59–2.59)		0.66 (0.26–1.66)	
Martin *et al.* (1986)[c]	F	2.60 (1.20–5.70)	3.40		al,b,d,e,f,m,o
Svendsen *et al.* (1987)[d]	M		1.61 (0.96–2.71)	1.40 (0.80–2.50)	a,al,b,c,m,o,s
Butler (1988)[e]	F	1.03 (0.62–1.72)	1.40 (0.51–3.84)		a,m
Palmer *et al.* (1988)	F	1.20			-
Sandler *et al.* (1989)	F		1.19 (1.04–1.36)		a,h,m,s
Hole *et al.* (1989)[f]	F	1.65 (0.79–3.46)			a,b,c,m,o,s
	M	1.73 (1.01–2.96)			
Jackson (1989)[d]	F		3.75 (1.15–12.19)	1.55 (0.48–5.03)	a,m,s
	M		1.06 (0.39–2.91)	1.80 (0.94–3.46)	
Humble *et al.* (1990)	F		1.59 (0.99–2.57)		a,b,c,m,o
Dobson *et al.* (1991)	F		2.46 (1.47–4.13)	0.66 (0.17–2.62)	a,m
	M		0.97 (0.50–1.86)	0.95 (0.51–1.78)	
LaVecchia *et al.* (1993)	F	1.27 (0.52–3.09)	1.36 (0.46–4.05)		a,b,c,d,f,m,o,s, +
	M	1.09 (0.47–2.53)	1.09 (0.39–3.01)		
Layard *et al.* (1995)	F	0.99 (0.84–1.16)			a,m,r
	M	0.97 (0.73–1.28)			
LeVois and Layard (1995)	F	1.03 (0.98–1.08)	1.04 (0.99–1.09)		a,m,r
(CPS-I)	M	0.97 (0.90–1.05)	0.98 (0.91–1.06)		
Mannino *et al.* (1995)	F + M		1.12		a,h,m,r,s

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Table 2. Relative risk estimates (95% CI) for heart disease among lifelong nonsmokers. (continued)

Study	Sex	Relative risk (95% CI) Spouse ever smoked	Spouse current smoker	Workplace exposure	Covariates adjusted for[a]
Muscat and Wynder (1995)	F	1.33 (0.59–2.99)		1.00 (0.40–2.50)	a,b,r,s
	M	1.38 (0.70–2.75)		1.20 (0.60–2.20)	
Tunstall-Pedoe *et al.* (1995)[g]	F + M		1.37 (1.07–1.75)		a,b,c,h,m
Ciruzzi *et al.* (1996)	F + M		1.43 (0.90–2.00)		a,b,c,d,f,o,s
He *et al.* (1996)[h]	F	1.38 (0.67–2.81)		1.85 (0.86–4.00)	a,b,c,f,o
Steenland *et al.* (1996)[i]	F	1.03 (0.91–1.18)	1.10 (0.96–1.27)	1.06 (0.84–1.34)	a,al,b,d,e,m,
	M	1.10 (0.99–1.22)	1.22 (1.07–1.40)	1.03 (0.89–1.19)	o,s, +
Kawachi *et al.* (1997)	F		1.71 (1.03–1.84)	1.68 (0.81–3.47)	a,al,b,c,d,e,f, m,o, +

[a] Covariates adjusted for: a = age, al = alcohol, b = blood pressure/hypertension, c = cholesterol, d = diabetes, e = exercise, f = family history of heart disease/hypertension, h – housing/urban-rural (in spousal analyses), m = marital status (in spousal analyses), o = obesity/weight, r = race, s = social class/education/income, + = other risk factor(s).

[b] Workplace data not given in Lee *et al.* (1986) but calculated from the source data (Lee *et al.*, 1995a).

[c] Spouse ever smoked data not given in Martin *et al.* (1986) but provided by Wells *et al.* (1988).

[d] Data for fatal and non-fatal CHD.

[e] Data for spouse-pairs cohort only; the AHSMOG cohort included ex-smokers.

[f] Updated results cited by Wells *et al.* (1994).

[g] Data for all CHD.

[h] Workplace results from He *et al.* (1994).

[i] Data for spousal cohorts based on Table 2 of Steenland *et al.* (1996).

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mon control group (details available on request). All data extracted and derived were independently checked.

The data extracted and considered further in this review are presented in Table 2. Table 2 also shows the covariates that were adjusted for in analysis.

Meta-Analysis

Combined estimates of relative risk for the various indices of exposure were obtained by fixed-effects meta-analysis (Fleiss and Gross, 1991). In the case of spousal smoking, fixed effects meta-analysis was also applied to various subsets of studies. The meta-analyses presented show not only the combined relative risk estimate, its 95% CI and its statistical significance, but also results of a chi squared test of whether the individual relative risks being combined were heterogeneous. Because the fixed effects-method takes no account of other differences between studies, *e.g.*, in study quality or the precise index of exposure used, the combined relative risk estimates need to be interpreted with caution, especially when significant heterogeneity is present. Where heterogeneity is present, the preferred method of approach is to look for its sources, as recommended by Blair *et al.* (1995). However, results from random-effects meta-analyses are also sometimes presented, using the likelihood approach of Hardy and Thompson (1996).

Table 3 presents results of fixed and random effects meta-analyses for all the studies and the three indices of ETS exposure. The table also shows the number of relative risk estimates and studies combined and the number that are statistically significant.

Results for Workplace ETS Exposure

Eight studies have reported a total of 13 heart disease relative risks for workplace exposure, none of which are statistically significant. Although nine of the 13 relative risks are greater than 1.0, the combined estimate (1.08, 95% CI 0.97-1.20) is not significantly elevated and there is no evidence of heterogeneity between studies. The data do not therefore provide reliable evidence that workplace ETS exposure is associated with an increased risk of heart disease.

This conclusion is at variance with that of an unconvincing recent overview by Wells (1998). Wells omits the workplace data presented by Lee (1995a), includes data for combined ex-smokers and lifelong nonsmokers from Butler (1985), uses a doubtful index of study quality which rates studies with higher relative risks more highly and fails properly to consider sources of potential bias such as publication bias, misclassification of smoking habits and confounding by other risk factors. Such sources of potential bias are considered below, where the far more extensive results for spousal ETS exposure are discussed in detail.

Results for Spousal Smoking

The data in Table 2, summarized in Table 3, show some evidence of an association between spousal smoking and risk of heart disease. The results do not

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Table 3. Meta-analyses of heart disease data for three indices of ETS exposure.

	Index of ETS exposure						
	Spouse ever smoked[a]			Spouse current smoker[b]			Workplace
	Male	Female	Combined	Male	Female	Combined	Combined
Number of relative risk estimates[c] (studies)	11 (11)	17 (17)	30 (20)	11 (11)	17 (17)	30 (20)	13 (8)
Number significant at 95% level							
Positive	2	5	8	3	5	9	0
Negative	0	0	0	0	0	0	0
Fixed-effects meta-analysis							
Relative risk	1.04	1.07	1.07	1.07	1.08	1.08	1.08
95% CI	0.99–1.11	1.02–1.11	1.03–1.10	1.00–1.13	1.04–1.12	1.05–1.12	0.97–1.20
Significance of relative risk	N.S.	<0.01	<0.001	<0.05	<0.001	<0.001	N.S.
Heterogeneity chisquared	15.68	36.03	58.27	18.59	33.79	58.08	9.92
Degrees of freedom	10	16	29	10	16	29	12
Significance of heterogeneity	N.S.	<0.01	<0.01	<0.05	<0.01	<0.01	N.S.
Random-effects meta-analysis[d]							
Relative risk		1.21	1.18	1.15	1.23	1.20	
95% CI		1.05–1.50	1.08–1.33	1.02–1.36	1.09–1.53	1.11–1.35	
Significance of relative risk		<0.01	<0.001	<0.05	<0.001	<0.001	

Note: N.S. Not significant ($p \geq 0.05$).

[a] Using current smoking where ever smoking not available.

[b] Using ever smoking where current smoking not available.

[c] Palmer *et al.* (1988) and Mannino *et al.* (1995), which did not provide estimates of 95% CI, are not included in the meta-analyses.

[d] Random-effects meta-analyses only shown where the heterogeneity chisquared is statistically significant.

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vary significantly by sex and are rather similar for the two indices of spousal ETS exposure. For the sexes combined, fixed-effects meta-analysis gives relative risk estimates of 1.07 (95% CI 1.03-1.10) for "spouse ever smoked" and of 1.08 (95% CI 1.05-1.12) for "spouse current smoker". However, there is significant ($p < 0.001$) heterogeneity between the study estimates. Using random-effects meta-analysis, which gives less weight to the larger studies, the overall relative risk estimates (RRs) increase to 1.18 (95% CI 1.08-1.33) for "spouse ever smoked" and 1.20 (95% CI 1.11-1.35) for "spouse current smoker".

Random-effects meta-analysis is of limited value as it provides no information on why the between-study heterogeneity is occurring. To gain insight into this, Table 4 presents results for "spouse ever smoked" showing how relative risks vary according to various aspects of the studies. (Results for "spouse current smoker" showed similar patterns and are not reported in detail here.) There is significant heterogeneity for most factors considered. Thus, RRs are clearly lower in studies that (i) are large, (ii) are conducted in the USA, (iii) are published recently, (iv) concern fatal heart disease, (v) have dose-response data available, and (vi) actually use spousal smoking as the index (rather than "nearest equivalent" indices like smoking in the household).

Table 4 also compares results by a study quality index. This index aimed to classify studies with obvious major weaknesses or that have not demonstrated their scientific validity as of "worse quality", and other studies as of "better quality". "Worse quality" studies included (i) studies reported only as abstracts or dissertations and not published in peer reviewed journals, (ii) studies of less than 100 heart disease cases, which suffer from excessively variable results and are likely to be unrepresentative due to publication bias, which affects small studies much more than large studies, (iii) the Dobson et al. (1991) study, which had a clear non-comparability in data collection between cases and controls, and (iv) the Tunstall-Pedoe et al. (1995) study, where the ETS exposure index used was shown to be particularly susceptible to bias. "Better quality" studies had markedly lower relative risks than "worse quality" studies.

Many significant variations in relative risk in Table 4 arose because three recently published large US studies (Layard, 1995; LeVois and Layard, 1995; Steenland et al., 1996) had all reported RRs close to unity. As a form of sensitivity analysis, the meta-analyses were repeated excluding these three studies. The results (details not shown) now provided no evidence of heterogeneity, except as regards study quality and study size. Accordingly, it seemed useful to present RRs for heart disease in three groups:

1. The three recently published "better quality" studies with more than 1000 cases

2. The seven "better quality" studies with less than 1000 cases

3. The 13 "worse quality" studies

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Table 4. Fixed-effects meta-analyses of heart disease for ever smoking by the spouse by level of various study-related factors.

Factor	Level	No. of estimates	Relative risk (95% CI)	Significance	Heterogeneity
Continent	USA	16	1.05 (1.01–1.08)	<0.01	<0.001
	Europe	7	1.34 (1.11–1.61)	<0.01	
	Asia	2	1.18 (0.96–1.44)	N.S.	
	Other	5	1.59 (1.22–2.08)	<0.001	
Publication date	1984–88	7	1.22 (1.04–1.44)	<0.05	<0.001
	1989–94	11	1.29 (1.17–1.43)	<0.001	
	1995–96	12	1.03 (1.00–1.07)	N.S.	
Study size	<100	8	1.54 (1.21–1.95)	<0.001	<0.001
	100–999	14	1.33 (1.18–1.50)	<0.001	
	1000 +	8	1.04 (1.00–1.07)	<0.05	
Study quality[a]	"Better quality"	18	1.05 (1.01–1.08)	<0.01	<0.001
	"Worse quality"	12	1.48 (1.28–1.72)	<0.001	
Study type	Case-control	14	1.11 (0.99–1.24)	N.S.	<0.05
	Prospective	14	1.05 (1.02–1.09)	<0.01	
	Cross-sectional	2	1.45 (1.15–1.84)	<0.01	
Endpoint	Fatal	17	1.05 (1.01–1.08)	<0.01	<0.001
	Other	13	1.42 (1.23–1.64)	<0.001	

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Table 4. Fixed-effects meta-analyses of heart disease for ever smoking by the spouse by level of various study-related factors. (continued)

Factor	Level	No. of estimates	Relative risk (95% CI)	Significance	Heterogeneity
Confounders considered	Yes	23	1.06 (1.03–1.10)	<0.001	N.S.
	No	7	1.19 (1.01–1.40)	<0.05	
Dose-response data available	Yes	18	1.04 (1.01–1.08)	<0.05	<0.001
	No	12	1.27 (1.15–1.40)	<0.001	
Spousal smoking[b] the actual index	Yes	20	1.04 (1.01–1.07)	<0.05	<0.001
	No	10	1.31 (1.19–1.44)	<0.001	

Note: N.S. Not significant ($p \geq 0.05$).

[a] See text for definition of study quality.

[b] In six studies spousal smoking was not recorded and the nearest equivalent index, usually based on smoking in the household, was used instead.

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Relative risk estimates vary strikingly between the three groups, the "worse quality" studies showing about a 50% increase in risk, the smaller "better quality" studies about a 25% increase and the larger "better quality" studies hardly any increase (Table 5). The heterogeneity **between** the three groups of studies is massively significant, but **within** each group, there is no evidence of heterogeneity.

Dose-Response Data

Twelve studies have provided 16 sets of dose-response data, mainly based on cigarettes per day smoked by the spouse (Table 6). Again, the results massively differed between the three groups of studies. Of the seven data sets from the "worse quality" studies, six reported RRs that increased monotonically with dose, with five finding a statistically significant positive trend. Of the three data sets from the smaller "better quality" studies, all found monotonic increases and two found significant positive trends. However, **none** of the ten data sets from the larger "better quality" studies showed either a monotonic increase or a trend, reemphasising the massive heterogeneity.

Sources of Bias that May Affect the Data for Spousal Smoking

Misclassification of Smoking Habits

For lung cancer, bias resulting from smokers being misclassified as nonsmokers may result in overestimation of RRs reported for spousal smoking, perhaps by 10% or more (Lee and Forey, 1996). The bias strongly depends on the magnitude of the excess risk associated with ever having smoked. This is substantially higher for lung cancer than heart disease, perhaps by a factor approaching 10. All other things being equal, it might therefore be expected that misclassification bias would only inflate heart disease spousal smoking RRs by 1 or 2%. However, other things may not be equal. Misclassification rates are particularly high in patients with diagnosed heart disease advised by their doctor to give up smoking (Lee, 1988), so subjects claiming to be nonsmokers may include some smokers particularly at risk of subsequent death from heart disease.

Support for this comes from a Danish prospective study (Suadicani *et al.*, 1997) in which self-reported smoking habits were recorded and serum samples taken for cotinine determination, prior to an 8-year follow-up period. Cumulative heart disease incidence in self-reported nonsmokers with cotinine levels above 100 ng/ml, a level inconsistent with nonsmoking, was 17.9%, based on five cases. This incidence was not only higher than in self-reported nonsmokers with cotinine levels below 100 ng/ml (3.1% based on 43 cases), but was 4.0 times higher (95% CI 1.8-9.1) than that in self-reported current smokers with cotinine levels above 100 ng/ml (4.3% based on 72 cases).

Misclassification corrections for lung cancer have accounted for cotinine levels in misclassified current smokers tending to be lower than in properly classified current smokers, although perhaps not in Asian populations (Lee, 1995b; Lee and Forey, 1995). Corrections have also accounted for misclassified

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Table 5. Fixed effects meta-analyses of heart disease, showing marked contrast in results between three groups of studies.

Exposure index/ group	No of estimates	Relative risk (95% CI)	Significance	Heterogencity Chi squarcd (df) and p	
				Within	Between
Ever smoking by the spouse					
3 recent large studies of "better quality"[a]	6	1.02 (0.99–1.06)	N.S.	4.06 (5) N.S.	34.92 (2) <0.001
7 other studies of "better quality"[b]	12	1.23 (1.13–1.35)	<0.001	5.83 (11) N.S.	
13 studies of "worse quality"[c]	12	1.48 (1.28 - 1.72)	<0.001	13.45 (11) N.S.	
Current smoking by the spouse					
3 recent large studies of "better quality"[a]	6	1.04 (1.00–1.08)	<0.05	8.95 (5) N.S.	32.49 (2) <0.001
7 other studies of "better quality"[b]	12	1.24 (1.13–1.35)	<0.001	5.83 (11) N.S.	
13 studies of "worse quality"[c]	12	1.52 (1.31–1.77)	<0.001	10.80 (11) N.S.	

Note: N.S. Not significant ($p \geq 0.05$). See text definition of "better quality"; large = more than 1000 deaths/cases.

[a] Layard (1995); LeVois and Layard (1995); Steenland *et al.* (1996).

[b] Hirayama (1984); Lee *et al.* (1986); Sandler *et al.* (1989); Hole *et al.* (1989); LaVecchia *et al.* (1993); Muscat and Wynder (1995); Kawachi *et al.* (1997).

[c] Other studies listed in Table 2 except Palmer *et al.* (1988) and Mannino *et al.* (1995) where CI were not provided.

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Table 6. Heart disease risk in relation to extent of exposure to spousal smoking separated by group of study.

Study	Sex	Spousal exposure index	Exposure levels	Relative risk by exposure level	Significance of trend
Large studies with more than 1000 cases					
Layard (1995)	M	Ever	0 1–14 15–34 35+	1.00 0.76 1.07 0.92	No
	F	Ever	0 1–14 15–34 35+	1.00 0.85 1.15 1.06	No
Layard and LeVois (1995)	M	Current	0 1–19 20–39 40+	1.00 0.99 0.89 0.72	No
(CPS-I)	F	Current	0 1–19 20–39 40+	1.00 1.04 1.06 0.95	No
Steenland *et al.* (1996)	M	Current	0 1–19 20 21+	1.00 1.33 1.17 1.09	No
(CPS-II)	F	Current	0 1–19 20 21–39 40+	1.00 1.15 1.07 0.99 1.04	No
No					
"Better quality" studies with less than 1000 cases[a]					
Hirayama (1984)	F	Ever	0 1–19 20+	1.00 1.10 1.31	Yes
Hole *et al.* (1989)	F	Ever	None Low High	1.00 2.09 4.12	Yes
La Vecchia *et al.* (1993)	M + F	Current	0 1–14 15 +	1.00 1.13 1.30	No
Kawachi *et al.* (1997)	F	Current	None Occasional Regular	1.00 1.58 1.91	Yes
"Worse quality" studies[a]					
Svendsen *et al.* (1987)	M	Current	0 1–19 20 +	1.00 1.20 1.75	No
Jackson (1989)	M	Current	None Low High	1.00 1.30 0.90	No
	F	Current	None Low High	1.00 2.10 7.50	Yes
Tunstall-Pedoe *et al.* (1995)	M + F	Current	None Little Some Lot	1.0 1.2 1.5 1.6	Yes
Ciruzzi *et al.* (1996)	M + F	Ever	0 1–20 21+	1.00 1.27 1.41	Yes
He *et al.* (1996)	F	Ever	0 1–20 21 +	1.00 2.30 6.86	Yes

[a] See text for description of study quality classification.

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ex-smokers tending to have smoked less and given up longer ago than properly classified ex-smokers (Lee, 1988; Lee and Forey, 1995). They have not adjusted for the fact that having the disease diagnosed by a doctor, coupled with advice to give up smoking, may increase the likelihood of denying smoking. This possibility is much more relevant for heart disease than lung cancer and suggests our tentative preliminary bias estimate of only 1 or 2% might be much too low. The much higher heart disease risk seen by Suadicani et al. (1997) for misclassified vs. non-misclassified smokers supports this suggestion, though more data are needed. While it is very difficult to adjust reliably for bias, one certainly cannot conclude misclassification bias is irrelevant, especially when the excess risk for spousal smoking, ignoring misclassification (see Table 3) is only 7 or 8%.

Confounding

ETS exposure is associated with an increased prevalence of many adverse health factors (Thornton et al., 1994; Emmons et al., 1995; Matanoski et al., 1995). Uncontrolled confounding may therefore bias upward estimates of the relationship between ETS and heart disease. However, not all factors will necessarily cause upward bias; alcohol consumption is positively related to ETS exposure (Thornton et al., 1994) but, at least in moderate amounts, it is negatively related to heart disease risk (Rimm et al., 1996).

Many of the ETS and heart disease studies paid only limited attention to confounding variables. Thus, about half ignored the classical coronary risk factors of blood pressure, cholesterol and body mass index, while very few took into account such factors as exercise, race, alcohol, diabetes, family history of heart disease or hypertension, or diet.

The danger of failing to take into account relevant dietary variables is well illustrated by the unsoundly based claim of Tribble *et al.* (1993) that chronic smoke exposure may reduce ascorbic acid level pools in passive smokers. This was based on the observation that nonsmokers exposed to ETS had a mean plasma ascorbic acid level (53 μmol/l) that was 24% less than that (70 μmol/l) in unexposed nonsmokers, completely ignoring the fact that the ETS-exposed nonsmokers had a similarly, 27%, reduced dietary intake of vitamin C (104 vs. 142 mg/day).

To estimate the bias due to uncontrolled confounding from the data published for the studies is extremely difficult. Often studies present only two relative risk estimates for an ETS exposure index, either totally unadjusted or adjusted for both age and a range of other variables so that effects of specific adjustments cannot be isolated. However, an attempt was made to study the available information (Table 7). Where the effects of confounding due to age and those due to other risk factors could be separately identified, there was some suggestion that age adjustment usually tended to increase relative risk estimates while adjustment for other risk factors tended to decrease them. The data also suggested that, where adjustment for the classical risk factors had been carried out, the relative risk estimate tended to be decreased. Many of the effects of adjustment shown in Table 7 were strikingly large. Of the 23 values,

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Table 7. Effects of adjustment for confounding variables on relative risks for spousal smoking and heart disease.

Factors adjusted for	No of estimates	Effects of adjustment on relative risk[a]
Age	5	**0.76**, 1.08, 1.12, 1.16, **1.22**
Factors other than age	4	**0.77**, 0.87, 0.92, 1.19
Age and one factor	8	0.93, 0.93, 0.94, 0.96, 0.96, 0.99, 1.04, **1.53**
Age and multiple factors	6	**0.68, 0.77**, 1.04, 1.10 1.14, **1.70**

[a] The table shows the ratio of the relative risk adjusted for the factors named to the relative risk not adjusted for the factors. Adjustments which increased or decreased the relative risk by a factor of 1.2 or more are emboldened. The data include results for both current and ever smoking.

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seven (in bold face in the table) increased or decreased the RR estimate by 20% or more. Considering the overall data for spousal smoking only suggests an increased relative risk by 7 or 8%, and considering the minimal control for confounding variables in many studies, it is readily apparent uncontrolled confounding could be an important contributor to the association.

Publication Bias

In the past, the literature on ETS and heart disease has clearly been greatly affected by publication bias. Garfinkel (1981) presented results relating spousal smoking to lung cancer from the ACS CPS-I study. It was apparent that this million person prospective study would allow similar analyses for heart disease based on very many deaths in nonsmokers. Although we were told by the ACS in the 1980s that such analyses had been conducted, even now they have not published their findings. Only when, years later, two independent scientists obtained the data and published their own analyses (LeVois and Layard, 1995) did it become apparent in the literature that here was a huge study showing no association whatsoever with ETS exposure. There is no reason to distrust their results, since their conclusions re CPS-I align with what we were told earlier, and since their analyses of CPS-II, in the same paper, produced answers very similar to those later reported by the ACS (Steenland et al., 1996), using a slightly different approach. It is striking that Steenland et al. (1996) did not even refer to the CPS-I results when citing the available literature, so perpetuating the publication bias.

While the existence of further unreported million person studies is unlikely, there are reasons for believing some publication bias may still affect the literature. First, there is the striking tendency for spousal smoking RRs to be higher in small studies (Tables 4 and 5). Second, some findings have been published years ago as abstracts or theses, with no proper published paper ever appearing later. Third, many prospective studies continue data collection, but a number have not reported updated findings. Finally, the total literature is sparse considering heart disease is much more common than lung cancer in a nonsmoker, and the literature on ETS and lung cancer is so extensive.

Other possible sources of bias. Lack of comparability of cases and controls was only severe in one study (Dobson et al., 1991) and is unlikely to have caused marked bias to the overall heart disease RR estimates. Recall bias may be more important, because spousal smoking RRs were higher for case-control than prospective studies, and because of the findings of Tunstall-Pedoe et al. (1995). In that study, prevalences of CHD and angina were unassociated with level of serum cotinine, but were associated with self-reported extent of recent ETS exposure. As the authors suggest, the exposure data may well be biased, subjects with symptoms of disease exaggerating exposure. Although these results cast doubt on self-reported data on extent of recent ETS exposure, they do not necessarily indicate responses to questions on spousal smoking are similarly invalid. Nevertheless, the possibility of recall bias remains.

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Errors in diagnosing heart disease are likely, especially since many prospective studies relied on death certificates with no independent confirmation of diagnosis. It is unclear whether errors are random. Tunstall-Pedoe et al. (1995) presented relative risk estimates associated with ETS and with cotinine separately for "diagnosed CHD", where the subject reported a medical diagnosis of angina, myocardial infarction, coronary thrombosis, or heart attack, and for "undiagnosed CHD", based on tests carried out at the time of interview. There was no association of serum cotinine with undiagnosed CHD, but a strong association with diagnosed CHD. The two associations should be similar, if heart disease is truly affected by ETS exposure. The conflicting results might have arisen because ETS exposure was associated with the extent of reporting existing, medically diagnosed, disease, or of symptoms to the doctor.

Plausibility

The large relative risks reported in some studies are difficult to tally with the relatively modest association between active smoking and heart disease, with relative risk estimates typically observed to be less than 2.0 (U.S. Surgeon-General, 1989; Doll *et al.*, 1994). It seems clear that average ETS exposure involves a substantially lower "dose" of any smoke constituent than obtained from average active smoking (Scherer *et al.*, 1989). This is underlined by recent reports (Robinson *et al.*, 1996; Ogden, 1996) that heavy smokers receive considerably higher ETS exposure than do passive smokers.

Conclusions Contrasted with Those of Glantz and Parmley and Others

We conclude that the epidemiological evidence relating ETS to heart disease is most unconvincing. There is no significant association with ETS exposure in the workplace. There is striking evidence of variation in spousal smoking relative risk estimates between three recent very large "better quality" studies which found no clear evidence of any increased risk at all, seven other "better quality" studies but generally involving less than 1000 cases which suggested about a 25% increase in risk, and the remaining studies, classified as of "worse quality", which suggested about a 50% increase in risk. Furthermore, the studies are susceptible to various sources of bias, including misclassification of smoking habits, uncontrolled confounding by other risk factors, recall bias and publication bias.

While one very recent review (Australian NHMRC, 1997) agrees with us that non-causal explanations are possible for the weak association of ETS with heart disease observed in epidemiological studies, other recent reports (Law *et al.*, 1997; California EPA, 1997; Wells *et al.*, 1998) agree with the view of Glantz and Parmley (1995) that they do indicate a causal relationship. However, there are some obvious weaknesses in these reviews.

One notable feature of those reviews concluding that ETS causes heart disease is that they seek to ignore the evidence presented for CPS-I by LeVois and Layard (1995) and for the National Mortality Followback Survey (NMFS) by Layard (1995). Law *et al.* (1997) reject both studies because Layard and LeVois

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are consultants to the tobacco industry and because their analysis of CPS-II cited relative risks different from those reported by Steenland *et al.* (1996). Actually, both analyses reported similar findings, a small decrease in risk for ex-smoking spouses and a small, non dose-related increase for current smoking spouses. The "differences," also referred to by California EPA (1997), arose as LeVois and Layard followed precedent in concentrating on the index "spouse ever smoked" while the ACS emphasized results for "spouse current smoker." In CPS-I risk was not elevated for either index. If Law *et al.* wish to reject analyses by tobacco consultants, they should , to avoid publication bias, have analyzed the CPS-I data themselves, but they notably failed to do this.

Wells (1998) rejected LeVois and Layard (1995) as being superseded by the more detailed analysis by Steenland *et al.* (1996) made of the same data set. Wells does not point out that Steenland *et al.* did not even consider CPS-I! He also rejects Layard (1995) for a variety of reasons, including use of 100% surrogate response and use of an index of exposure "spouse smoked >100 cigarettes in total at any time during the various marriages" which was regarded as insensitive. Since the percent of surrogate response was the same for cases and controls, and since the index of exposure used in some of the other studies is similar, the decision to reject, made *post hoc* in knowledge of the findings, seems highly dubious. Many studies with evident major weaknesses were not rejected.

The attention given by the other reviewers to possible sources of bias is also extremely inadequate. Glantz and Parmley (1995) do not even discuss sources of bias at all, while Wells (1988) pays very little attention to them. Law *et al.* (1997) dismiss smoking misclassification bias as unimportant, ignoring the evidence from Suadicani *et al.* (1997) that smokers denying smoking have a 4.0 times higher (95% CI 1.8–9.1) risk of heart disease than do smokers admitting smoking. They dismiss publication bias as unimportant, using an argument which only addresses whether it might explain the whole association. Though they give more consideration to the possibility of confounding, this is limited to only a few of the many heart disease risk factors.

Overall we see nothing in these reviews which affects our conclusion that the epidemiological evidence relating ETS exposure to heart disease does not provide convincing evidence of a causal relationship.

SOME GENERAL PROBLEMS IN CONDUCTING EXPERIMENTAL AND CLINICAL STUDIES

Before considering in detail the laboratory and clinical evidence that has been interpreted by Glantz and Parmley (1995) and others as adding strength to the argument that ETS exposure causes heart disease, it is important to realize that there are a number of problems that apply generally in conducting and interpreting experiments aimed at determining the effects of exposure to ETS.

One serious problem is that clinical studies cannot be conducted "blind". Physical and/or mental annoyance or irritation associated with ETS exposure

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may give rise to stress-related effects not directly attributable to any of the chemical components of ETS, such as increased pulse rate and blood pressure, reduced exercise tolerance, and various changes in blood chemistry. Glantz and Parmley (1995) seem generally to be unaware of this problem, assuming that any responses seen represent toxic effects of inhaled chemicals. Even in studies involving different levels of exposure to ETS, increasing annoyance with increasing exposure may lead to stress-related dose-response relationships.

Another problem is that many of the studies are difficult to interpret because of the extremely high levels of exposure that are used, and because exposure is not to ETS but to sidestream smoke or to mainstream smoke. It should be remembered that the question of interest is not to determine whether smoking causes heart disease, and still less whether tobacco smoke contains components that are cardiotoxic at high doses, but to determine whether exposure to realistic levels of ETS can cause relevant effects on the heart. Thus, for example, it is clear that increased COHb levels can lead to reduced exercise tolerance and to other effects attributable to reduced oxygen delivery and availability to vital tissues. However, ETS is only one of many sources of CO, and by no means the most important in many situations. Vehicular exhaust fumes, and domestic heating systems are, overall, far more important sources of CO with many attributable deaths in the case of defective heating systems. By comparison, rises in COHb levels in nonsmokers resulting from ETS exposure are usually trivial in extent and are readily reversed following cessation of exposure.

Confounding is another issue that has not been addressed properly, or even at all, in many of the human studies. A large number of risk factors have been associated with heart disease risk (Hopkins and Williams, 1981) and there is considerable evidence that the distribution of risk factors differs materially among nonsmokers according to their extent of ETS exposure (LeMarchand *et al.*, 1991; Thompson and Warburton, 1993; Thornton *et al.*, 1994; Emmons *et al.*, 1995; Matanoski *et al.*, 1995).

Finally, much of the evidence discussed below relates to endpoints with no proven, or even likely, association with atherogenesis. It is widely accepted that coronary heart disease is associated with atherosclerosis and consequential narrowing of the lumen of the arteries supplying the cardiac muscle. The development of atherosclerosis is a slow process that can begin in childhood and continue over many months or years. During the early stages of this process the disease is usually "silent" and the person affected is wholly unaware of its existence. Later the sufferer may or may not become aware of reduced exercise tolerance. Reduction in exercise tolerance may take the form of shortness of breath on exercise and/or actual chest pain (angina pectoris). Alternatively, a wholly unexpected occlusion of a coronary artery may give rise to the sudden onset of chest pain and delayed, or immediate, death. Chance clearly plays a part in whether, and how, coronary atherosclerosis gives rise to symptoms and/or causes death. The sudden blockage of an already diseased coronary artery may be due to thrombus formation or spasm, while the consequences of

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such occlusion vary according to which vessel is involved. If an artery supplies the neural conducting system of the heart, *i.e.* the atrioventricular bundle, vascular occlusion may lead to complete heart block and ventricular fibrillation which is quickly fatal. In these circumstances there may be insufficient time for changes recognisable by the pathologist as acute myocardial ischaemia to develop. Indeed the only proof that death was due to ventricular fibrillation may be electrocardiographic tracings in a continuously monitored patient.

Theoretically, as discussed below, disturbances of platelet function might be involved in the process of atherogenesis and/or in the sudden occlusion of an already diseased artery. However, whether the disturbance of function which predisposes to atheromatous change is the same as that which predisposes to sudden occlusion of an already diseased vessel is not clear.

For these several reasons it is unsound to assume that observations made in the very short term in humans or animals, particularly if they have healthy arteries, are relevant to risk of myocardial infarction.

EXPERIMENTAL AND CLINICAL STUDIES IN HUMANS

Effects of ETS on Oxygen Delivery, Processing, and Exercise

Glantz and Parmley (1995) state that the CO in ETS "displaces and competes with oxygen for binding sites on red blood cells." So it does, but does exposure to the CO in ETS influence the development of heart disease? The reduction in the amount of oxygen carried by the blood resulting from ETS exposure is small compared with that associated with climbing to moderately higher altitudes. Furthermore, the body rapidly adapts to reduced oxygen delivery and compensates for it by increasing the red blood cell count.

Glantz and Parmley (1995) cite studies by Allred *et al.* (1989) and Sheps *et al.* (1990) in which nonsmokers underwent exercise tolerance testing in differing exposure conditions as support for their statement that "people with existing heart disease show increasing electrocardiographic evidence of ischaemia and experience more arrythmias as carboxyhemoglobin increases, even at *low levels.*" However, these studies, though randomized and double blind, involved exposure to CO levels in the range 100-250 ppm, levels that are more than 10-fold higher than typically seen during real life ETS exposure. Moreover, Glantz and Parmley (1995) fail to mention that, in the study by Sheps *et al.* (1990), the lower exposure level of 100 ppm, which produced a COHb level of 4%, typical of *smokers* but not of nonsmokers exposed to ETS, was found not to increase the frequency of arrythmias.

Based on three studies (Aronow, 1978; Leone *et al.*, 1991, 1992; Khalfen and Klochkov, 1987) Glantz and Parmley (1995) also claim that ETS exposure affects performance on exercise testing and increases the risk of arrythmias in people with coronary heart disease. This evidence, and that reported in a similar later study by Mori et al. (1993), is unconvincing. The studies generally involved exposures higher than those typically experienced in real life, with no randomization of the order in which subjects were tested under the differing exposure conditions. Furthermore, the study by Aronow (1978), which only

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concerns smokers and ex-smokers to the exclusion of nonsmokers, is open to suspicion following reports of data falsification. An independent review of his work on heart disease and CO, conducted by the EPA, concluded that it could no longer be relied upon to formulate environmental standards (Mintz, 1983; Peterson, 1983).

The study by Leone *et al.* (1991) is cited by Glantz and Parmley (1995) as evidence that ETS exposure affects performance on exercise testing in healthy young adults. Another study they cite (McMurray *et al.*, 1985) only involved four nonsmokers and four smokers. On the other hand, Glantz and Parmley (1995) fail to cite a larger study by Pimm *et al.* (1978) which found few consistent changes in measures of lung volumes or in exercise responses as a result of ETS exposure. Khalfen and Klochkov (1987) also reported no significant effect of ETS exposure on exercise response in healthy subjects. We conclude that there is little or no evidence that realistic exposure to ETS measurably affects exercise tolerance, lactate production, cardiac function, ECG tracings, etc. in healthy persons. This is particularly clear under conditions in which time is allowed for adaptation to very slightly raised COHb levels.

Effect of Smoking on Compliance of Coronary Artery Walls

Glantz and Parmley (1995) refer to two studies concerning acute effects of smoking a single cigarette. Such studies, which report increased coronary vascular resistance (Quillen *et al.*, 1993) and decreased compliance of coronary artery walls (Kool *et al.*, 1993), probably relate to acute effects of nicotine exposure. They are unlikely to be of much relevance to the possibility that coronary artery atherogenesis results from the much lower exposure to nicotine in ETS.

Effects of Exposure to ETS on Blood Lipids

Glantz and Parmley (1995) cite five references (AHA, 1994; Moskowitz *et al.*, 1990; Pomrehn *et al.*, 1990; Moskowitz *et al.*, 1993; Feldman *et al.*, 1991) as evidence that "children of smoking parents have elevated levels of 2,3-diphosphoglycerate, an enzyme that increases the disassociation of oxygen from hemoglobin in red blood cells in an effort to compensate for chronic oxygen deprivation." In fact, only two of these five references (Moskowitz *et al.*, 1990, 1993) presented data comparing 2,3-diphosphoglycerate levels by parental smoking status, and both reported an association in boys but not girls. In neither of these studies was any adjustment made for differences in diet and socioeconomic status associated with parental smoking (Thornton *et al.*, 1994; Emmons *et al.*, 1995; Matanoski *et al.*, 1995). In any case, 2,3-diphosphoglycerate is not an enzyme.

Effects of ETS on Blood Leucocytes

Anderson *et al.* (1991) reported that exposure of healthy young nonsmokers to actively smoking individuals for three hours in a poorly ventilated room resulted in an increase in leukocyte counts, phorbol myristate acetate-activated

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luminol-enhanced chemiluminescence and neutrophil migration. Glantz and Parmley (1995), citing this study, note that neutrophils are an important element of the body's defences against infection and damage and that inappropriately activated neutrophils "release oxidants that can play a role in tissue damage in passive smokers." The results of Anderson *et al.* (1991) are potentially of more relevance to possible effects of ETS exposure on lung disease than to those on heart disease. In any case their findings, which are based on extremely small numbers of subjects, are difficult to interpret because of lack of information on diurnal variation in the parameters used and lack of control of potential confounding variables. Arguably, chemiluminescence measures smoke exposure rather than any health consequence of such exposure.

Other studies have examined the relationship of ETS to leukocyte counts. In one study (Bovill *et al.*, 1996) a trend toward higher counts in passive smokers did not reach statistical significance. In another, Green *et al.* (1993), in a study of 250 male factory workers reported no association of leukocyte counts with either reported ETS exposure or with cotinine level. The authors concluded that, if ETS exposure is associated with heart disease risk, it is not mediated through an effect on leukocyte count.

Effects of ETS on platelets

Glantz and Parmley (1995) note that activation of blood platelets "increases the likelihood of formation of a thrombus and can damage the lining of the coronary arteries and facilitate the development of atherosclerotic lesions". They cite a study by Burghuber *et al.* (1986) and a series of studies by Davis *et al.* (1985a, 1985b, 1986, 1987, 1989) as support for the view that "nonsmokers are much more sensitive to secondhand smoke than smokers and that very low levels of ETS exposure can have major impacts on nonsmokers' platelet activity". They also claim that "these data indicate that dose-based extrapolations from smokers to non-smokers using cigarette equivalents will grossly underestimate the risk to non-smokers of breathing secondhand smoke".

More recently, a review by Law *et al.* (1997) claims that "platelet aggregation provides a plausible and quantitatively consistent mechanism for the low dose effect (*i.e.*, the increased heart disease risk associated with ETS exposure they observed based on the epidemiological data)". As the basis for their argument they cite data from an epidemiological study by Elwood *et al.* (1991) in which a strong association was reported between measures of platelet aggregation and risk of heart disease, and also experimental evidence that acute changes in platelet aggregation following ETS exposure (Davis *et al.*, 1989) are of comparable magnitude to changes following smoking of one or two cigarettes (Davis et al., 1981, 1982, 1985a, 1985b, Schmidt and Rasmussen 1984, Blache *et al.*, 1992). In contrast, Law *et al.* (1997) regard any effect of ETS exposure on plasma fibrinogen, on high density lipoprotein cholesterol and on COHb to be so small that any resultant increased risk of heart disease would be imperceptible.

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In evaluating the claims of Glantz and Parmley (1995) and of Law *et al.* (1997), a number of points are relevant. First, conclusions reached in the literature regarding the role of enhanced platelet aggregation in IHD are far from unanimous (Maseri, 1995). Second, the study of Elwood *et al.* (1991) provides unconvincing evidence that platelet aggregation increased risk of heart disease. The study was of cross-sectional design relating *in vitro* platelet aggregation to the presence of heart disease and provides no information on future risk of heart disease in relation to platelet aggregation. As Elwood *et al.* themselves point out, "the increase in platelet sensitivity in some men with evidence of prevalent disease can, therefore, be a result rather than a cause of the ischaemic disease process".

Third, although acute smoking experiments have given conflicting data on platelet aggregation (Bierenbaum *et al.*, 1978; Taylor *et al.*, 1987; Vicardi *et al.*, 1988; Woolf, 1992), both Glantz and Parmley (1995) and Law *et al.* (1997) relied heavily and uncritically on the work of Davis *et al.* (1981, 1982, 1985a, 1985b, 1986, 1987, 1989). Gori (1995) has noted that Davis et al. used a non-standard assay, which is influenced by the procedure used to draw blood, the presence and kind of coagulant, centrifugation parameters, and other variables. There are many additional problems with interpretation of the study by Davis *et al.* (1985a) which claimed that the smoking of two cigarettes by 10 healthy male and 10 healthy female non-smokers increased platelet aggregation. Median plasma nicotine levels were not zero in the 10 men before they smoked, suggesting some of them were smokers, there was no control for the possibility of stress, no monitoring of blood pressure or aspirin taking and no control for dietary factors.

It is also remarkable that the arguments of Law *et al.* (1997) regarding acute effects of ETS exposure on platelet aggregation were based on only a single study. This study (Davis *et al.*, 1989) involved only 10 individuals and is subject to the same criticisms as the other studies by Davis and his colleagues. Furthermore, the researchers neither quantified nor controlled ETS exposure. Also, the study was unblinded, without cross-over, and took place in a hospital corridor near to or beside a lift-shaft, where exposure to airborne substances was likely.

Other studies (Sinzinger and Kefalides, 1982; Burghuber *et al.*, 1986; Schmid *et al.*, 1996) have reported effects of ETS exposure on platelet sensitivity *in vitro* to the anti-aggregatory activity of prostaglandins, but it is not known whether the method of measuring platelet formation accurately reflects platelet function *in vivo* or whether the observations are relevant to the risk of development of atherosclerosis.

There are no animal data that support the conclusion that ETS exposure increases the risk of thrombus formation because of an effect on platelet numbers or function. Evidence of adverse effects on platelet activating factor derived from studies on smoke extracts (Miyaura *et al.*, 1992) provide no direct support for the theory that ETS exposure is a risk factor for cardiovascular disease.

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Effects of ETS on Endothelium Function

Celermajer *et al.* (1996) conducted a study aimed at assessing endothelial function in the arteries of 78 young adults, all aged 15 to 30, with normal blood pressure and no evidence of diabetes or of hyperlipidaemia. Twenty-six were active smokers, 26 never smokers regularly exposed to ETS for at least 1 hour/day for 3 or more years and 26 never smokers not regularly exposed to ETS. The diameter of the brachial artery of each subject was measured by ultrasound under baseline conditions, during reactive hyperemia (produced by cuff inflation and release) and after sucking a nitroglycerine tablet (which has a vasodilatory effect on arteries). Flow-mediated dilatation was observed in all control subjects (mean 8.2%) but was significantly impaired in the passive smokers (mean 3.1%) and in the active smokers (mean 4.4%). In the group of passive smokers, flow-mediated dilatation was inversely related to the reported intensity of exposure to ETS. Dilatation induced by nitroglycerine was similar in all groups. The authors concluded that the passive smoking dose-related impairment of endothelium-dependent dilatation suggests early arterial damage, a suggestion echoed by Glantz and Parmley (1996).

The method of recruitment of subjects in the study by Celermajer *et al.*, involving friends and families of hospital staff, and the fact that the study was conducted under conditions of informed consent, introduces possibilities of bias. The self-reported data on ETS exposure is questionable, especially since flow-mediated dilatation in passive smokers, though related to reported ETS exposure, was not correlated with salivary cotinine level, a more objective index of actual exposure. Also, no data were collected on factors that might affect arterial responsiveness (*e.g.*, diet, alcohol, coffee, medicines, general indoor and outdoor air pollutants). Even if what the investigators observed actually was an effect of ETS exposure, it seems wildly speculative to assume that the findings are relevant to the longterm development of cardiovascular disease.

Effects of ETS on Atherosclerosis

According to one theory, endothelial damage by toxins predisposes to the adherence of platelets to the vessel wall. Without such damage prostacyclin produced by endothelial cells protects against the adherence of platelets. However once platelets become adherent they release mitogens, such as platelet-derived growth factor, which promote the proliferation of smooth muscle cells.

Glantz and Parmley (1995) cite Davis *et al.* (1989) as support for their claim that short-term exposure to ETS "significantly increases the appearance of anuclear endothelial cell carcasses in the blood" and that "the appearance of these cell carcasses indicates damage to the endothelium". In this experiment blood was obtained before and after ten healthy male nonsmokers sat for 20 min either in open hospital corridors where several patients were smoking or in a laboratory where smoking was prohibited. The numbers of dead endothelial cells per counting chamber rose in all ten subjects during ETS exposure,

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but did not materially change during the control period. Though statistically significant, the interpretation of this increase is not straightforward. Awareness of ETS exposure can cause stress, giving rise to catecholamine release with numerous resultant physiological changes. Davis *et al.* (1989) did not measure stress or see if stress in the absence of ETS exposure influences endothelial cell counts. It is theoretically possible that a quickening of the pulse and/or a rise in blood pressure and velocity secondary to stress would lead to a "flushing out" of dead endothelial cells from blood vessels. In other words exposure to ETS may not have damaged the vascular endothelium, but simply have led to the dislodgement of cells that had died earlier, either from natural apoptosis or as a result of prior exposure to a toxicant. It seems very unlikely that sitting by a smoker for 20 min in a hospital corridor could lead to a measurable increase in circulating dead anuclear endothelial cells as a direct consequence of exposure to tobacco-smoke constituents in the ambient air.

Glantz and Parmley (1995) note that adolescents whose parents smoke show lower levels of high density lipoprotein cholesterol (HDL-C) than children breathing clean air. Most of the relevant studies, whether reporting (Moskowitz *et al.*, 1990; Pomrehn *et al.*, 1990; Feldman *et al.*, 1991) or not reporting (Iscan *et al.*, 1996) a relationship of HDL-C with cotinine levels or with parental smoking, have not attempted to adjust their results for the well documented observation (Thornton *et al.*, 1994; Emmons *et al.*, 1995; Matanoski *et al.*, 1995) that the diets consumed by smoking and nonsmoking families tend to differ. Any differences in lipid parameters that were seen may well relate to diet rather than to ETS exposure. In this respect, it was notable that one study (Neufeld *et al.*, 1994), which did adjust for dietary fat intake, as well as other cardiovascular risk factors, found that such adjustment markedly reduced the significance of the association of HDL-C with passive smoking, from $p < 0.001$ to $p = 0.017$.

Moffatt *et al.* (1995) have reported lower HDL-C, HDL_2 and apoA-1 levels in 19 nonsmoking women exposed to ETS at work than in 9 nonsmoking women not so exposed. This study is limited by its very small size in relation to the large number of factors that may affect levels of the lipoproteins, by the failure to measure ambient levels of ETS components or other indoor air pollutants, and by the lack of any clearly established relationship between the lipoproteins measured and risk of heart disease.

Glantz and Parmley (1995) refer to the large cross-sectional study of Howard *et al.* (1994) as evidence that "passive smokers have significantly thicker carotid artery walls, in a dose-response relationship, than people who never were exposed to passive or active smoking." In this study, weekly ETS exposure of at least 1 hour was associated, in men and women aged 45 to 64, with an increase in intimal-medial thickness (IMT) of 0.017 mm in never smokers, the increase being reduced to 0.013 mm, but remaining statistically significant ($p = 0.003$), after adjustment for a range of other risk factors. In considering this evidence, various points should be made. First, Glantz and Parmley (1995) did not cite Tell *et al.* (1994), who reported no association of passive smoking with carotid artery wall thickness in older men and women, aged 65+, participating

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in the same study. Second, the dose-response relationship with extent of ETS exposure referred to by Glantz and Parmley (1995) was in fact only seen in men, no significant dose-response being seen in women despite the much larger sample of never smokers studied. Furthermore, interpretation is also limited by concerns relating to adequacy of control for diet and other confounding factors, misclassification of active smoking status and errors in self-reported ETS exposure. Also, as noted by California EPA (1997), the significance for health of the small increases in wall thickness is unclear. While Kawachi and Colditz (1996) argued that small differences in blood vessel diameter have disproportionately large effects on blood flow, the results of Salonen and Salonen (1993) suggest that any effect of ETS exposure on risk of myocardial infarction via increased IMT is likely to be very small. Salonen and Salonen reported an 11% increase in risk of myocardial infarction associated with a 0.1 mm increase in IMT, suggesting less than a 2% increase in risk associated with the 0.013-mm increase in IMT claimed by Howard *et al.* (1994).

More recently, Diez-Roux *et al.* (1995) have reported results in which household smoke exposure data obtained in 1975 was linked to the carotid artery IMT measurements obtained 12 to 14 years later in the study by Howard *et al.* (1994). Diez-Roux *et al.* reported slightly higher IMT values in those never smokers reporting ETS exposure. However, the difference was not statistically significant, and the study was weakened by the very large proportion of subjects excluded because of missing or inconsistent information on smoking status, missing information on IMT or risk factors, or difficulty in linking the 1975 and 1987-1989 databases.

Howard *et al.* (1996, 1998) have also reported, based on further IMT readings, that the progression of IMT over a 3-year period is also linked to ETS exposure. However, again the relationship was not statistically significant in never smokers. We conclude that the carotid artery data, though suggestive, do not provide compelling evidence that ETS exposure affects risk of heart disease.

It is appropriate to ask whether IMT can be used to measure atherosclerosis. According to Bots *et al.* (1996) ultrasound imaging cannot discriminate between the intimal layer and the medial layer of the vessel wall. In other words it cannot distinguish between intimal thickening due to atherosclerotic plaque formation and non-atherosclerotic thickening due or mainly due to medial changes. Furthermore, as pointed out by Wendelhag *et al.* (1992), intimal-media thickening can result from hemodynamic changes which involve increase in wall tension in a vessel in the absence of atherosclerotic changes.

Heiss *et al.* (1991) used an IMT of 1600 microns as the cut-off point below which such measurements would not be regarded as indicative of plaque formation. Later Grobbee and Bots (1994) proposed the use of 900 microns as the cut-off point. However, Howard et al's studies involved measurements within the range of only 626 to 657 microns. Even if the annual increments in thickness proposed by Howard *et al.* (1998) as a response to exposure to ETS were correct, it would take a very long time for the thickness to rise to a level considered by these earlier investigators as possibly indicative of atherosclerosis.

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Another very important question concerns the relationship between measurements of carotid IMT and coronary artery disease. According to Adams *et al.* (1995), IMT of the common carotid artery is only weakly correlated with the extent and severity of coronary artery disease as assessed angiographically.

Next, serious questions may be raised about the relationship between the 3-year effects of ETS exposure on IMT (*i.e.*, 5.9 microns) and the limits of resolutions of, and variably in, ultrasound measurements. Measurements of IMT to the nearest 10 microns (occasionally 10 microns) have generally been assumed to be close to the limits of ultrasound measurement resolution. Indeed inter-observer and inter-operator variations in the range of 5-10% (equivalent to 30 to 70 microns) have been reported (Adams *et al.*, 1995).

Finally it is important to point out that the quality and reliability of the ETS exposure data used by Howard *et al.* (1998) were poor, being based on crude and unverified self-reported estimates. Furthermore Howard et al. (1998) did not find any evidence of a dose-response relationship between ETS exposure and increased IMT in their study.

EXPERIMENTAL ANIMAL STUDIES

Effect of Exposure to Mainstream Smoke on Production of Adenosine Triphosphate by the Myocardium

In their abstract, Glantz and Parmley (1995) state that "passive smoking . . compromises the myocardium's ability to use oxygen to create adenosine triphosphate." This conclusion is actually based on a single study (Gvozdjak *et al.*, 1987, Gvozdjakova *et al.*, 1992) in which male rabbits were exposed to mainstream cigarette smoke in an incubator. The authors provided no details on numbers of rabbits or on level of exposure to CO or other smoke components and relate their results only to effects of smoking, with passive smoking not being discussed. Stress from being confined in cages and of noise from fans may have contributed to the effects reported, and there is a need for parallel observations on rabbits exposed to other substances under similar conditions.

Atherosclerosis — Studies of Effects of Polycyclic Aromatic Hydrocarbons (PAHs)

Glantz and Parmley (1995) cite their earlier review (Glantz and Parmley, 1991) for evidence that PAHs accelerate the development of atherosclerosis. Studies in chickens or White Carneau pigeons from various laboratories (Albert *et al.*, 1975; 1977; Penn *et al.*, 1981; Revis *et al.*, 1984) have shown that repeated huge doses by intramuscular injection of certain carcinogenic PAHs, such as benzo(*a*)pyrene (B(*a*)P), dimethylbenz(*a,h*)anthracene (DMBA), or 3-methylcholanthrene, result in increased aortic plaque formation compared with solvent-only injected controls. According to Albert *et al.* (1975), exposure to X-irradiation or to injections of chemical carcinogens of other types (*e.g.*, 2-acetylaminofluorene, *N*-methyl-*N*- nitro-N-nitrosoguanidine) did not affect plaque formation. Neither did exposure to benzo(*e*)pyrene, a non-carcinogen-

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ic analogue of B(*a*)P (Revis *et al.*, 1984). Studies using tritiated thymidine indicated that plaque growth in carcinogen treated birds is a function of cell proliferation (Albert *et al.*, 1977). However, the plaques in birds exposed to carcinogenic PAH were indistinguishable morphologically from plaques in untreated older birds. This does not suggest a specific effect of PAH on plaque development.

Birds given repeated very high doses of B(*a*)P or DMBA showed greatly reduced body weight gain, indicating a profound effect on their overall nutritional status (Albert *et al.*, 1977). However, the influence of nutritional status on plaque growth is uncertain and was not controlled for.

Results of studies of aortic plaques taken from women who are heterozygous with respect to glucose-6-phosphate dehydrogenase isoenzymes (Benditt and Benditt, 1973; Pearson *et al.*, 1980) are consistent with the possibility that individual plaques are derived from single cells. However, to suggest, as do Glantz and Parmley (1991, 1995) and Penn *et al.* (1986), that the plaques are in reality benign smooth muscle tumours of the aortic wall is not supported by their histopathological appearance.

Citing the data of Penn *et al.* (1992), Glantz and Parmley (1995) appear to contradict themselves when they write "The carcinogens appear to be acting as a promoter to facilitate the development of plaques rather than as initiator of plaques." This implies that they do not think that mutations due to carcinogens in ETS initiate the formation of plaques which they earlier suggested might be smooth muscle tumours.

Since atherosclerosis has not been described following PAH exposure in numerous studies in rodents and other non-avian species, it is unlikely that humans risk developing coronary heart disease from exposure to very low concentrations of PAH carcinogens in ambient air.

Atherosclerosis — Studies Involving the Exposure of Rabbits to ETS

Zhu *et al.* (1993) exposed groups of rabbits on a high-cholesterol diet for 10 weeks to levels of ETS sufficient to produce average air carbon monoxide levels of 60.2 ppm (high-dose), or 18.8 ppm (low-dose) compared to 3.1 ppm (unexposed). They reported increased atherosclerotic involvement of the aorta and pulmonary artery and decreased bleeding times in the ETS exposed groups. Glantz and Parmley (1995) claim that this study demonstrates "that short-term exposure to ETS significantly speeds the atherosclerotic process." The study is questionable for a number of reasons. First, as Benowitz (1991) opined, after reviewing the available data, studies on cholesterol-fed rabbits "are of questionable relevance to human atherosclerosis." Furthermore, arterial plaque formation in the *aorta* and *pulmonary artery* of rabbits fed for just 10 weeks on an atherogenic diet may well be an inappropriate model for *coronary artery* atherogenesis in humans. Intimal fatty plaques do not necessarily progress to atherosclerotic plaques involving the media as well as the intima. Fatty plaques which arise in the intima of the aorta in milk-fed human babies disappear after weaning on to a more varied diet. Zhu *et al.* (1993) made no attempt to study effects

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of ETS exposure on the coronary arteries. Second, the ETS exposure levels studied by these investigators greatly exceeded human exposure levels occurring in everyday life. Even the so-called "low-dose" was over twice as high as ETS-exposed nonsmokers normally encounter. Third, rabbits experience severe stress when confined in exposure chambers, especially if there is noise from fans. In the experiments reported by Zhu *et al.* (1993) the high- and low-dose ETS-exposed rabbits were confined in cages of unstated size within chambers (eight rabbits per 3.58 m^3 chamber) equipped with three fans per chamber. No attempt was made to assess the potential contribution of confinement/noise stress to the effects seen. It should also be noted that although the percentage of the aortic and pulmonary artery surface areas covered by "atherosclerotic lesions" was significantly increased in the high-dose group, differences between the low-dose and control groups were not statistically significant. Furthermore, there were no significant differences between groups in serum triglycerides, cholesterol or high-density lipoprotein cholesterol.

Sun *et al.* (1994) conducted a study in which 32 cholesterol-fed rabbits were randomly divided into four groups: ETS with the βblocking agent metoprolol, ETS without metoprolol, non-ETS with metoprolol and non-ETS without metoprolol. Rabbits in the ETS groups were exposed to sidestream smoke from 4 cigarettes per 15 minutes, 6 hours a day, for 10 weeks. ETS exposure resulted in a significant increase in lipid deposits in the aorta and pulmonary artery, while metoprolol treatment resulted in a significant decrease. As the two effects were independent, Glantz and Parmley (1995) argued that the effects of ETS were not mediated by an increase in catecholamine release. The limitations of this study were very similar to those of the study by Zhu *et al.* (1993). Again, exposure to ETS was extremely high, with CO levels of 67 ppm in the chambers.

Atherosclerosis — Studies Involving the Exposure of Cockerels to ETS

Penn *et al.* have conducted a series of experiments in which young cockerels were exposed, by inhalation or injection as appropriate, for 16 weeks to carbon monoxide (Penn *et al.*, 1992), sidestream cigarette smoke at a higher dose (Penn *et al.*, 1993), or at a lower dose (Penn *et al.*, 1994), to the tobacco-specific nitrosamine NNK (present in the tar fraction) or to the volatile alkene 1,3-butadiene (Penn and Snyder, 1996), or to solubilized concentrated tar or to the PAH carcinogen DMBA (Penn *et al.*, 1996). In all these studies, the aortas were examined, following exposure, for presence and extent of plaque. While no effects were reported as a result of exposure to carbon monoxide, increases in plaque were noted from sidestream smoke at both doses, from 1,3-butadiene and from DMBA. Glantz and Parmley (1995) argue that the studies on sidestream smoke support their view that "short-term exposure to ETS significantly speeds the atherosclerotic process." Although the studies on cockerels, unlike the rabbit studies, do not involve cholesterol feeding, they do have a number of other weaknesses.

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In the first place there is no obvious support for the assumption that aortic plaque formation, which occurs naturally in birds as they get older, or its enhancement by short-term experimental procedures, has any relevance to human coronary artery atherosclerosis. Atherosclerotic plaques in human arteries contain lipid-laden foam cells and are very different from the spontaneous plaques in young cockerel aortas which are composed of smooth muscle cells and collagen and do not contain lipid. Second, the concentration of ETS used in the first sidestream study (Penn *et al.*, 1993) was very high (Coggins, 1994), involving CO levels of about 35 ppm. Even in the second study (Penn *et al.*, 1994), where cockerels were exposed for six hours per day to the steady-state combustion of one rather than five cigarettes, CO levels exceeded those commonly reported in nightclubs and bars. Also, the investigators did not control for stress due to multi-housing, *e.g.*, by conducting studies in free-range birds or by including a group exposed to a non-ETS irritant. Nor did they monitor levels of stress hormones, or examine adrenal glands histologically.

It should be noted also that the statistical analysis seems to have been incorrectly conducted. In the first sidestream study (Penn *et al.*, 1993), which involved groups of 30 exposed and 12 unexposed cockerels, no significant difference was seen between the groups in plaque incidence or distribution when comparisons were made on a per bird basis. Only when analysis was based on data for individual segments of aorta were differences in plaque index (plaque area/luminal circumference) reported to be significant. However, the statistical methods erroneously treated all the observations as independent, effectively counting results from the same bird multiple times instead of once. The same gross statistical error, which massively inflates significance, has been made in the other sidestream study (Penn *et al.*, 1994).

These weaknesses preclude any conclusion being drawn from the results of Penn *et al.* regarding possible effects of even high dose ETS exposure. Clearly, they also preclude any inferences being drawn regarding the relevance of specific components of smoke, such as CO, NNK or 1,3-butadiene, to any possible effect of ETS on the atherosclerotic process.

It should also be noted that Glantz and Parmley (1995) claim that ETS exposure "for a relatively brief time (corresponding to about 0.4% of their life span)" significantly accelerated the development of plaque in cockerels. There seems an obvious error here, since an exposure of 16 weeks is 0.4% of a lifespan of 77 years, much longer than cockerels in fact live.

Atherosclerosis — Experimental Studies Involving the Exposure of Rats to ETS

The most reliable information with regard to the subacute toxicity of ETS in rats comes from a standard 90 day inhalation study conducted by Coggins *et al.* (1993). In that study male Sprague-Dawley rats were exposed to either no ETS (sham exposure), a low dose considered typical of human exposure (2.9 ppm CO), a mid-dose representing "extreme" human exposure (9.3 ppm CO)

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or a high-dose equivalent to unrealistically high exaggerated exposure (55.1 ppm CO). Coggins *et al.* (1993) saw no meaningful between-group differences in body weight, organ weights or clinical parameters. The only effect observed during detailed histopathological evaluation was in the nose, a change consisting of epithelial hyperplasia in the rostral turbinates of rats in the high-dose group. Although this change was seen in rats killed after 4, 28, and 90 days exposure, it was not evident in rats exposed to the high dose for 90 days and then killed after a further 90-day exposure-free period. No pathological changes whatsoever were seen in the blood vessels or in the hearts of rats exposed to ETS at any of the three dose levels.

The study of Coggins *et al.* (1993) needs to be taken into account in the interpretation of the complex and contrived experimental rat studies described by Zhu *et al.* (1994, 1996). In these, untreated rats and rats that had been exposed to unrealistically high levels of ETS throughout 6 hours per day for 6 weeks were subjected surgically to left coronary artery occlusion for 35 minutes followed by reperfusion. Myocardial infarcts were larger in previously ETS-exposed rats than in non-ETS exposed rats and the presence of L-arginine in the perfusate had the effect of reducing the adverse effect of ETS exposure on infarct size.

If, as seems clear from the results reported by Coggins *et al.* (1993), even extremely high exposure to ETS has no effect on the coronary vasculature, how can the findings of Zhu *et al.* (1994, 1996) be regarded as indicative of increased risk of the development of atherosclerosis either in rats or in humans?

Roberts *et al.* (1996) studied the effect of exposing healthy rats to ETS on the rate of accumulation of LDL cholesterol in the carotid artery. They found that plasma taken from rats that had been exposed to high concentrations of ETS increased the accumulation of LDL cholesterol in the walls of the carotid arteries of other rats following its intra-arterial perfusion. On the basis of this short-term test using a non-inbred strain of rats (Sprague-Dawley) the investigators speculate that repeated exposures to ETS may represent important early events in atherogenesis. However, it is difficult to see how such a speculation, based on an ultra short-term study in the carotid arteries of a species that does not develop coronary atherosclerosis, could be usefully investigated further in relation to determining the causation of heart disease in man.

An effect of tobacco smoke exposure on cholesteryl esterase activities and associated accumulations of cholesteryl esters in the aortas of rats exposed to ETS has been reported by Maehira *et al.* (1995). This is difficult to interpret because the investigators provide no information on the composition of the atmospheres to which rats were exposed or on the uptake of ETS components. Furthermore, they provide no information concerning the effects of stress on the parameters which they measure. In any case, the relevance of lipid accumulation in the aortic intima of rats in the course of a study of only 4 or 12 weeks' duration to the development of coronary artery atherosclerosis in humans is dubious.

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The Possible Role of Free Radicals in ETS and Ischemic Heart Disease: Studies in Dogs, Rats, and Hamsters

Glantz and Parmley (1995) claim that "passive smoking worsens the outcome of an ischemic event in the heart through the activity of free radicals during reperfusion injury." In support of this claim they cite a study by Przyklenk (1994) in which dogs were subjected to an occlusion of the left anterior descending coronary artery for 15 minutes followed by a 3-hour period of reperfusion. Nicotine given before the period of occlusion adversely affected recovery during the period of reperfusion. Nicotine given one hour after reperfusion also affected cardiac function, even when the dose given was too low to affect heart rate, arterial pressure, or blood flow. Glantz and Parmley (1995) also cite studies by van Jaarsveld *et al.* (1992a, 1992b) in which rats exposed to dilute mainstream smoke from two cigarettes a day for two months showed impaired mitochondrial function during reperfusion injury.

While studies of the effect of exposure to ETS or its constituents on the recovery of animals subjected to surgical occlusion of coronary arteries might be relevant to patients with existing coronary artery occlusion, they throw no light on the role of free radicals in coronary artery atherogenesis. The studies by van Jaarsveld *et al.* (1992a, 1992b) are particularly poorly conceived. Thus there was no measure of the extent of exposure of rats to any smoke constituent, no information on the response to non-ETS chemicals (*e.g.*, simple irritants), the animals were exposed to mainstream smoke and not to ETS, and the COHb levels of smoke-exposed and non-exposed rats did not differ. In particular, the finding in the second of these studies (van Jaarsveld *et al.*, 1992b) that antioxidant vitamin supplementation particularly protected smoke-exposed rats from myocardial change following a 10-minute period of ischaemia followed by reperfusion must be regarded as uninterpretable.

According to McCusker and Hoidal (1990), exposure of hamsters to ETS led to enhanced activity of antioxidant enzymes (superoxide dismutase and catalase) in their pulmonary macrophages. The fact that the activities of these enzymes in nonsmokers is lower than in smokers is interpreted by Glantz and Parmley (1995) as implying that nonsmokers exposed to ETS are at higher risk than smokers from free-radical damage. This speculation fails to consider questions of dose, frequency of exposure and the probability that extra protection from free-radical damage is unrequired under realistic conditions of ETS exposure when the extent of free-radical damage is immeasurably small. Anyway, any tobacco smoke associated free-radical damage that may occur is more likely to be relevant to lung disease than to heart disease.

Myocardial Infarction: Studies in Dogs with Surgically Occluded Coronary Arteries

Glantz and Parmley (1995) cite two animal studies as evidence that "ETS promotes more tissue damage following myocardial infarction." One study (Prentice *et al.*, 1989) involved 10 dogs subjected to surgically induced coronary artery occlusion, five of which had previously been exposed to cigarette

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smoke in an inhalation chamber sufficient to give COHb levels as high as 27%. The brief abstract reported that the mean size of infarcts was significantly ($p < 0.025$) higher in the smoke-exposed dogs than in the controls. Clearly, validation of the techniques involved and the results of a larger study are needed. In any case, the findings seem relevant neither to ETS exposure nor to atherogenesis. The other study was that by Zhu *et al.* (1994) in rats, which has already been considered above. There is no obviously close relationship between spontaneous coronary vascular occlusion in humans as a result of atherosclerosis and disease resulting from the sudden clamping of a non-diseased coronary artery in previously healthy laboratory dogs or rats.

DISCUSSION

In light of the evidence of increased risk of heart disease in smokers compared to nonsmokers, it is appropriate to consider whether or not there is any increased risk of heart disease as a consequence of exposure to environmental tobacco smoke. However, there are several reasons why it is difficult to obtain a clear answer to this question.

First is the fact that epidemiology is beset with difficulties when it comes to investigations of low levels of risk. This is particularly so in relation to diseases with a long latent interval, diseases with multi-factor aetiologies, and diseases where genetic constitution affects susceptibility, and under circumstances where there can be no precise measurements of exposure to a suspect agent over the long term. Secondly, in the case of ETS one is faced with something that has a distinctive smell and which many people find irritant to the eyes and upper respiratory tract. Thirdly is the fact that the association between smoking and risk of lung cancer has put fear in the minds of many people and added to the fervour which anti-smoking campaigners bring to the task of persuading people not to smoke.

Given these difficulties there is a need to be exceedingly careful, as a scientist, when designing and interpreting the results of studies aimed at investigating the possible relationship between exposure to ETS and risk of coronary heart disease.

In the present paper we have tried to review the available epidemiological, clinical and experimental data as objectively as possible and have reached the conclusion that there is no clear evidence that exposure to ETS increases the risk of development of coronary heart disease.

Since Glantz and Parmley have taken a leading role, in their much cited 1995 paper, in bringing together what they considered as evidence for an association between ETS exposure and heart disease, we have used that paper as a starting point for this review.

The fact that there is no obviously appropriate animal model for coronary artery atherosclerosis poses enormous difficulties for those who seek to study the mechanisms involved in the aetiology of coronary heart disease in man. Nevertheless this does not excuse the readiness with which many investigators have been willing to extrapolate from ultra short-term studies in humans or

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laboratory animals to reach conclusions about the contribution of long-term ETS exposure to coronary artery atherosclerosis.

It is pertinent to begin any study of the possible role of ETS in the aetiology of CHD by considering what the disease is and how it can kill. In this regard others have focused on two components of ETS, nicotine and carbon monoxide (CO), and have proposed a variety of mechanisms by which these constituents of ETS might act. However, it is clear to us that CHD is not a single disease entity in terms of either the immediate manifestation of symptoms or prognosis and that genetic constitution has a major impact. Dietary factors are also major determinants of CHD and numerous other factors (*e.g.*, oral contraceptives) are risk factors for cardiovascular disease generally.

It is also pertinent to question whether exposure to ETS is really equivalent to exposure to very low doses of cigarette smoke as inhaled by the smoker. Cigarette smokers who inhale receive not only a gradual build up of plasma nicotine levels but also pulse doses of nicotine. These have neuro-pharmacological effects which contribute to the pleasure of smoking. By contrast pipe smokers, cigarette smokers who do not inhale, nicotine gum suckers, tobacco chewers, wearers of nicotine patches and nonsmokers exposed to ETS only experience a gradual rise of plasma nicotine. This difference is relevant to any consideration of the possible association between exposure to nicotine and risk of CHD and it is noteworthy that pipe smokers show little extra risk of CHD compared with cigarette smokers who inhale (Wald *et al.*, 1981; Carstensen *et al.*, 1987). In the case of exposure to the nicotine present in ETS, although the route of exposure is inhalation, the doses are too small to have any measurable neuropharmacological effects. Certainly none have been recorded.

Benowitz (1991) reviewed the possible ways in which nicotine may predispose to CHD. In his view a causal link between cigarette smoking and CHD is well established but the pathophysiology underlying the association is not. Catecholamines released from the adrenal medulla in response to nicotine increase heart rate and raise blood pressure. These effects can put an increased strain on an already diseased heart. By contrast a healthy heart has plenty of functional reserve to deal with such increased strain. Catecholamine release is, in fact, a normal physiological response to danger.

If nicotine predisposed to increased circulating levels of blood lipids, damaged the endothelial cells that line blood vessels, or increased risk of thrombosis by activating blood platelets, it would be plausible that exposure to nicotine *per se* could lead to damage of the coronary vessels which supply the heart muscle both with nutrients and with oxygen. However, according to Benowitz (1991), there is no clear or unequivocal evidence that nicotine has any of these effects either in man or in laboratory animals.

As for the possibility that CO in ETS can cause CHD in nonsmokers, one cannot rely solely on arguable plausibility. The affinity of CO for hemoglobin, with resultant reduced capacity of the blood to transport oxygen, plausibly explains the reduction in exercise tolerance following exposure to the gas. There are many environmental sources of CO other than tobacco smoke and CO is

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generated within the body. Exercise increases the rate of elimination of CO provided that ambient CO levels are low: rest decreases it.

Even when ETS levels are high, blood levels of neither CO nor nicotine rise nearly as much in nonsmokers as they can do in smokers. These considerations indicate that the risk of CHD in nonsmokers exposed to ETS cannot be reliably predicted on the basis of data for active smokers.

Evidence that persons with existing heart disease exhibit reduced exercise tolerance when they are exposed to CO without their knowledge or to ETS with their knowledge (because they can smell it) tells one nothing about the possible role of CO or ETS in coronary atherogenesis.

We have not seen any convincing evidence that exposure to ETS has effects on blood lipids, fibrinogen, leucocytes, platelets, or endothelial function that predisposes to the development of coronary artery atherogenesis.

The reported increase in circulating anuclear endothelial cell carcasses following ultra short-term and unmeasured exposure to ETS is an uninterpretable observation because of a complete lack of background information on the endpoint and what other exposures are associated with it.

Only one of the animal studies discussed above is realistic in terms of possible exposure to ETS. This is the 90-day rat study by Coggins *et al.* (1993). In many other studies exposure was excessive and to mainstream tobacco smoke rather than ETS. In most the endpoint was aortic atheroma and not coronary artery atherosclerosis or occlusion. The effects of ETS exposure on the extent of myocardial infarction following the clamping of coronary arteries in previously healthy rats or dogs strikes us as a parody of legitimate experimentation, producing wholly uninterpretable results. The use of cholesterol feeding to enhance the effects of other agents is less objectionable but only really meaningful if coronary artery atherosclerosis as distinct from aortic atherosclerosis is the endpoint.

All in all we conclude that animal studies have contributed very little to our understanding of coronary artery atherogenesis in humans and have certainly not provided any persuasive evidence that exposure to ETS predisposes to atherogenesis in humans.

CONCLUSIONS

We find Glantz and Parmley's conclusion that ETS increases the risk of heart disease unjustified because:-

1. There is no persuasive evidence that passive exposure to either nicotine or CO causes atherosclerosis.

2. Claims based on the results of short-term studies in humans or laboratory animals that exposure to CO, nicotine or ETS increase the risk of development of atherosclerosis are not supported by data from long term studies in which *atherosclerosis of the coronary arteries* constitutes the end point.

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3. Although exposure to CO might reasonably reduce exercise tolerance and impair cardiac muscle performance in persons with existing evidence of cardiac ischaemia, the ready reversibility of these effects renders it unlikely that exposure to CO leads to progressive heart disease.

4. It is plausible that the pharmacodynamic effects of nicotine might temporarily increase the work-load of the heart and that this might show up as reduced exercise tolerance in persons with existing heart disease.

5. The plausibility of toxicity is heavily dependent on dose and in realistic circumstances the doses of CO or nicotine from ETS exposure are rarely high enough to give rise to any measurable effects.

6. The epidemiological evidence relating to ETS heart disease is unconvincing. There is no significant association with ETS exposure in the workplace. Though the overall data do show a significant association with spousal smoking, the association is weak and could well be a result of various forms of bias (e.g. misclassification of smoking habits in nonsmokers which might be more relevant than has been thought, uncontrolled confounding, publication bias and recall bias). Hitherto disproportionate attention has been paid to small studies with many identified weaknesses. Three recent studies without major apparent weaknesses, each involving more than 1,000 cases of heart disease in nonsmokers, found no real evidence of any increased risk in relation to spousal smoking.

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